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Oscillatory neural networks underlying resting-state, attentional control and social cognition  
task conditions in children with ASD, ADHD and ASD+ADHD

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## Abstract

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are common and impairing neurodevelopmental disorders that frequently co-occur. The neurobiological mechanisms involved in ASD and ADHD are not fully understood. However, alterations in large-scale neural networks have been proposed as core deficits in both ASD and ADHD and may help to disentangle the neurobiological basis of these disorders and their co-occurrence. In this study, we examined similarities and differences in large-scale oscillatory neural networks between boys aged 8-13 years with ASD ( $n = 19$ ), ADHD ( $n = 18$ ), ASD+ADHD ( $n = 29$ ) and typical development (Controls,  $n = 26$ ). Oscillatory neural networks were computed using graph-theoretical methods from electrophysiological (EEG) data collected during an eyes-open resting-state and attentional control and social cognition tasks in which we previously reported disorder-specific atypicalities in oscillatory power and event-related potentials (ERPs). We found that children with ASD showed significant hypoconnectivity in large-scale networks during all three task conditions compared to children without ASD. In contrast, children with ADHD showed significant hyperconnectivity in large-scale networks during the attentional control and social cognition tasks, but not during the resting-state, compared to children without ADHD. Children with co-occurring ASD+ADHD did not differ from children with ASD when paired with this group and vice versa when paired with the ADHD group, indicating that these children showed both ASD-like hypoconnectivity and ADHD-like hyperconnectivity. Our findings suggest that ASD and ADHD are associated with distinct alterations in large-scale oscillatory networks, and these atypicalities present together in children with both disorders. These alterations appear to be task-independent in ASD but task-related in ADHD, and may underlie other neurocognitive atypicalities in these disorders.

Keywords: autism spectrum disorder (ASD); attention-deficit/hyperactivity disorder (ADHD); comorbidity; functional neural networks; EEG

## 1. Introduction

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are common and impairing neurodevelopmental disorders which frequently co-occur (Baird et al., 2006; Grzadzinski, Dick, Lord & Bishop, 2016; Polanczyk, de Lima, Horta, Biederman & Rohde 2007; Simonoff et al., 2008). ASD is characterised by social-communication deficits and restricted, repetitive behaviours, while ADHD is characterised by impairing inattention, hyperactivity and impulsivity (American Psychiatric Association, 2013). The neurobiological mechanisms underlying ASD, ADHD and their co-occurrence are not fully understood. One approach to investigating this issue is to examine overlapping and distinct neurobiological atypicalities in ASD and ADHD, and to explore how those atypicalities manifest in individuals with both disorders (Taurines et al., 2012).

Following this approach, in our previous work we used electroencephalography (EEG) to examine neurocognitive profiles in children with ASD without co-occurring ADHD, ADHD without co-occurring ASD, co-occurring ASD+ADHD, and typical development. We found that ASD and ADHD were associated with disorder-specific atypicalities in several cognitive domains, including frequency-specific decreases in resting-state oscillatory power (Shephard et al., 2018) and altered event-related potential (ERP) markers of attentional control (Tye et al., 2014a) and social cognition (Tye et al., 2013; 2014b), suggesting that distinct neurocognitive mechanisms are involved in each disorder. Children with ASD+ADHD showed both ASD- and ADHD-related atypicalities, indicating that disorder-specific alterations in resting-state, attentional control and social cognition are summed in an additive manner in children with both conditions (Shephard et al., 2018; Tye et al., 2013; 2014a; 2014b, see also Groom et al., 2017; Lundervold et al., 2017 for similar findings in independent samples of children). In the current study, we sought to further understand the neurobiological mechanisms involved in ASD, ADHD and their co-

occurrence. In particular, we aimed to investigate whether the atypicalities in resting-state, attentional control and social cognition we reported previously were underpinned by disorder-specific or overlapping alterations in task-related functional connectivity. Further, we sought to investigate whether such functional connectivity alterations are restricted to particular cognitive domains or are task-independent in these disorders; atypical connectivity that is task-independent might provide a converging platform for understanding the varied neurocognitive profiles associated with ASD and ADHD.

Atypicalities in functional connectivity have been proposed as core neurobiological factors in both ASD and ADHD (Barry, Clarke, McCarthy & Selikowitz, 2002; Courchesne & Pierce, 2005; Just, Cherkassky, Keller & Minshew, 2004; Stam & Van Straaten, 2012). Functional connectivity refers to the coordination of activity across distributed brain regions to form a functional neural network. Functional networks are highly organised, with segregated brain regions specialised for particular functions and functional connections integrating specialised regions to enable complex cognitions and behaviours (Bullmore & Sporns, 2009; Sporns, Chialvo, Kaiser & Hilgetag, 2004). Neuronal oscillations synchronised across different brain regions are believed to underlie the formation of functional networks, with the frequency of oscillatory synchrony (delta, 1-3Hz; theta, 4-8Hz; alpha, 8-12Hz; beta, 12-30Hz; gamma, 30-100Hz) mediating different functional characteristics, e.g. high-frequency synchrony is thought to govern local, bottom-up processing networks while slower-frequency synchrony is associated with larger-scale top-down processing networks (Siegel, Donner & Engel, 2012; Uhlhaas & Singer, 2006).

In ASD, widespread functional underconnectivity (Just et al., 2004) or increased local with decreased global connectivity (Courchesne & Pierce, 2005) have been hypothesised to underpin disruptions in social-communication and higher-order cognitive processing and thus contribute to the hallmark symptoms of the disorder. Studies using EEG or

magnetoencephalography (MEG) to investigate oscillatory functional networks in resting-state and cognitive task conditions have provided mixed support for these hypotheses. In the resting-state, children and adults with ASD have shown reduced synchrony between oscillatory signals measured at long-range sites coupled with increased short-range synchrony (Ghuman, van den Honert, Huppert, Wallace & Martin, 2017; Peters et al., 2013), supporting the increased local/decreased global hypothesis. Decreased long-range synchrony with unaltered or decreased short-range synchrony has also been reported in the resting-state in children with ASD compared to controls (Dickinson et al., 2018; Kikuchi et al., 2015), supporting the underconnectivity hypothesis. These alterations involved the theta and/or alpha frequencies, suggesting networks mediated by slow-to-mid frequency oscillations may be most susceptible to disruption in ASD. However, contradictory resting-state findings have also been reported in children and adults with ASD (Kitzbichler et al., 2015; Vakorin et al., 2017). Findings have been more consistent in oscillatory connectivity measured during cognitive task conditions. In tasks measuring aspects of social cognition, including face processing, emotion recognition and joint attention, children and adults with ASD have shown reduced local and/or global synchrony in alpha and/or beta frequency bands compared to controls (Jaime et al., 2016; Khan et al., 2013; Mennella, Leung, Taylor & Dunkley, 2017; but see Luckhardt, Kröger, Cholemkery, Bender & Freitag, 2017; Mamashli et al., 2018). Similarly, reduced theta and/or alpha range oscillatory synchrony in large scale networks underlying executive and attentional control processes, including set-shifting, response inhibition and working memory, have been reported in children and adults with ASD compared to controls (Doesburg, Vidal & Taylor, 2013; Kenet et al., 2012; Urbain et al., 2016). Of note, only one of these studies examined oscillatory neural networks across more than one task domain. Jaime et al. (2016) reported reduced oscillatory synchrony in the alpha range between centro-temporal scalp sites in adolescents with ASD during both joint

attention and resting-state conditions, suggesting hypoconnectivity may be a pervasive deficit that occurs independent of task domain in ASD.

In ADHD, increased local with decreased global network function (Stam & Van Straaten, 2012), and widespread hyperconnectivity with more restricted long-range hypoconnectivity resulting in reduced segregation and specialisation of functional brain networks (Barry et al., 2002), have been suggested to impair efficient processing in attentional and regulatory control circuitry, resulting in the inattentive, hyperactive and impulsive symptoms of the disorder. Consistent with the latter hypothesis, resting-state M/EEG studies have reported widespread hyperconnectivity, particularly in the theta range and involving frontal connections, combined with restricted fronto-posterior hypoconnectivity in the alpha range in children ADHD compared to typically developing controls (Barry et al., 2002; Barry, Clarke, McCarthy, Selikowitz & Johnstone, 2005; Robbie et al., 2016; but see Murias, Swanson & Srinivasan, 2006). Similarly, during tasks measuring attentional control and working memory, children and adults with ADHD have shown increased oscillatory synchrony in the theta, alpha and beta frequencies in frontal-frontal and frontal-posterior connections (Heinrichs-Graham et al., 2014; Lenartowicz et al., 2016; Silberstein et al., 2016). However, others have reported patterns of increased local with decreased global synchrony (Liu, Chen, Lin, & Wang, 2015) or hypoconnectivity between fronto-posterior connections without evidence of hyperconnectivity (Mazaheri et al., 2010) in children with ADHD during attentional control tasks, which may reflect differences in methods used to compute and analyse connectivity and/or the particular attentional control paradigms used across these studies. To our knowledge, no published work has examined oscillatory neural networks across cognitive domains or during social cognition tasks in ADHD. It is therefore unclear whether similar connectivity alterations underlie resting-state and attentional control atypicalities in ADHD, and whether these extend to the social



cognition impairments that are increasingly being recognised as part of the disorder (Bora & Pantelis, 2016).

In summary, previous work indicates there may be distinct functional network abnormalities in ASD and ADHD, with widespread hypoconnectivity and an imbalance in local/global networks in ASD and widespread hyperconnectivity with limited fronto-posterior disconnection in ADHD. Still, findings are variable and not all studies controlled for co-occurring symptoms of ASD and ADHD, which might explain some of the heterogeneity. Further, several of the ASD studies have been conducted with samples with broad age-ranges (e.g. 6-21 years in Kitzbichler et al., 2016; 2-10 years in Dickinson et al., 2018), while the ADHD studies have tended to focus on narrower age-ranges (e.g. 8-12 years in Barry et al., 2002; 2005; Mazaheri et al., 2010). This variation in age-range complicates drawing comparisons between ASD and ADHD across studies because age-related changes in neural circuits are well documented (e.g. Boersma et al., 2011) and connectivity measures in children of different ages are not necessarily comparable. Moreover, only one study (Jaime et al., 2016) examined functional connectivity across more than one experimental task, and further research examining neural network alterations across cognitive domains in the same individuals is needed to confirm whether connectivity alterations are task-specific or whether they reflect generalised neural processing dysfunctions in ASD and ADHD. Finally, no published work has directly compared oscillatory neural networks between individuals with ASD, ADHD and ASD+ADHD. It is therefore unclear whether overlapping or distinct atypicalities characterise ASD and ADHD and how they present in the co-occurring form.

In this study we aimed to address these issues by comparing oscillatory neural networks during resting-state, attentional control and social cognition task conditions between children aged 8-13 years with ASD without co-occurring ADHD, ADHD without ASD, co-occurring ASD+ADHD and typically developing controls. While we previously

reported analyses of resting-state oscillatory power (Shephard et al., 2018) and ERP correlates of attentional control and social cognition (Tye et al., 2013; 2014a) in these data, the current analyses were novel and focused on neural network function underlying the previously reported neurocognitive atypicalities. We tested 1) whether ASD would be associated with hypoconnectivity and/or increased local with decreased global connectivity, 2) whether ADHD would be associated with hyperconnectivity and/or increased local with decreased global connectivity, and 3) whether ASD+ADHD would show both ASD- and ADHD-related atypicalities in oscillatory networks or whether individuals in this group would show a unique profile of altered connectivity. Finally, we assessed whether these profiles of oscillatory connectivity were unique to or generalised across the three cognitive domains.

## 2. Materials and methods

### 2.1 *Participants*

Participants were boys aged 8-13 years with ASD ( $n = 19$ ), ADHD ( $n = 18$ ), ASD+ADHD ( $n = 29$ ), or typical development (Control group,  $n = 26$ ) (see Table 1 for group characteristics). All participants had normal or corrected-to-normal vision, IQ scores  $>70$  on the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), and were without neurological or neurodevelopmental conditions other than ASD and ADHD (excluding oppositional defiant disorder). Participants with ASD and/or ADHD were recruited from South London neurodevelopmental outpatient clinics and held a DSM-IV (American Psychiatric Association, 2000) clinical diagnosis of one or both disorders. Clinical research assessments were conducted to confirm pure or co-occurring diagnoses. ASD was diagnosed using the Social Communication Questionnaire Lifetime version (SCQ; Rutter, Bailey & Lord, 2003), Autism Diagnostic Interview-Revised (Lord, Rutter & Couteur, 2004) and

Autism Diagnostic Observation Schedule-Generic (Lord et al., 2000). ADHD was diagnosed using the Conners 3 Parent Short Form (Conners, 2008) and Parental Account of Childhood Symptoms (Taylor, Schachar, Thorley & Wieselberg, 1986). Children with ASD+ADHD met full diagnostic criteria for ASD and ADHD using these measures. Participants without neurodevelopmental or psychiatric diagnoses and without siblings with ASD or ADHD were recruited from local schools and forums for the Control group; all were screened for subclinical symptoms using the Strengths and Difficulties Questionnaire (Goodman, 1997), SCQ, and Conners. Participants taking medications other than stimulants were excluded from the study. Six boys with ADHD and six boys with ASD+ADHD were receiving stimulants; these children refrained from taking their medication for 48 hours before testing. A further 1 boy with ADHD and 1 boy with ASD+ADHD had previously received stimulants but were not taking any medication at the time of the study. All inclusion/exclusion criteria were established prior to data analysis, and we report all manipulations and all measures in the study. Ethical approval was obtained from the NHS National Research Ethics Service (NHS Wandsworth REC 08/H0903/161) and London Research & Development Departments. In accordance with the Declaration of Helsinki, parents provided written informed consent before study measures were conducted. Determination of sample size is described in our first published report in this sample (Tye et al., 2013).

[Table 1]

## *2.2 EEG acquisition and paradigms*

### *2.2.1 EEG data acquisition*

Participants completed a 90-minute task battery while their EEG was recorded from 62 Ag/AgCl active scalp electrodes placed according to the extended 10-20 system using an

ActiCHamp DC-coupled recording system (Brain Products, Munich, Germany). The data were referenced online to electrode FCz and sampled at 500Hz. Vertical and horizontal eye movements were recorded from electrodes above and below the left eye and at the outer canthi.

### *2.2.2 Resting-state paradigm*

The EEG task battery began with a six-minute eyes-open resting-state recording during which participants fixated on a dot on the opposite wall and minimised movements. We previously analysed the data from this task for effects of ASD and ADHD on oscillatory power ( $\mu\text{V}^2$ ) and found that ASD was associated with reduced theta (4-8Hz) and alpha (8-12Hz) power while ADHD was associated with reduced delta (1-3Hz) power (Shephard et al., 2018). In the current study, we conducted a novel re-analysis of these data to examine effects of ASD and ADHD on the extent and organisation of resting-state oscillatory networks (methods described in 2.3.2 below).

### *2.2.3 Attentional control paradigm*

Following the resting-state recording, participants completed a computerised cued-CPT task (CPT-OX; McLoughlin et al., 2010) to assess attentional and inhibitory control. This task is reported in full in our previous publication reporting effects of ASD and ADHD on ERP correlates of attention and inhibition (Tye et al., 2014a). Briefly, participants viewed letter-string stimuli (e.g. XDX) presented for 150ms every 1650ms. Cue stimuli (XOX, 80 trials) indicated that the next stimulus could either be a Target (OXO) for which participants were required to press a response-button (40 ‘Go’ trials), or a non-target (e.g. XDX) for which participants withheld their responses (40 ‘Nogo’ trials). Distractor stimuli (e.g. XHX,

ODO, 240 trials) were presented amongst the Cue, Go and Nogo stimuli to increase attentional demands.

For the current analysis of oscillatory neural networks, we included data for the Cue condition only (and not Go/Nogo conditions) for two reasons. First, our previous analysis of Cue-locked ERPs in this sample revealed alterations related to both ASD (altered preparatory processing indicated by enhanced amplitude of the Contingent Negative Variation (CNV) component) and ADHD (reduced attentional allocation to the Cue stimuli indicated by reduced amplitude of the Cue-P3 component), indicating that preparatory and attentional processes are important in understanding these disorders (Tye et al., 2014a). Second, the number of correct, artefact-free trials in the Go and Nogo conditions was low (<15 trials) for many participants in this sample, which resulted in insufficient data for reliable computation and analysis of oscillatory network indices. Thus, in the current study, we examined effects of ASD and ADHD on the extent and organisation of oscillatory neural networks underlying Cue processing in the CPT task, particularly focusing on the time-ranges corresponding to the Cue-P3 and CNV ERP components (described in section 2.3.3 below). Behavioural performance data for this task are presented in the Supplementary Materials; note that one child with ADHD and two children with ASD+ADHD were excluded from connectivity analyses due to producing excessive Go omission errors ( $\geq 70\%$  of Go trials), indicating poor attention and engagement with the task.

#### *2.2.4 Social cognition paradigm*

After the CPT task, participants completed a face processing paradigm in which they viewed upright and inverted female faces displaying direct or averted gaze to assess social cognition. Face stimuli (shown for 500ms) were preceded by fixation images (e.g. flags, cartoon characters, also displayed for 500ms) included to maintain the participant's interest.

Full task details are given in our previous report of ERP correlates of face and gaze processing in ASD and ADHD (Tye et al., 2013). For the current analysis of oscillatory networks, we focused on the upright and inverted face (with direct gaze) conditions, since these revealed the clearest ASD- and ADHD-related atypicalities in ERP markers of face processing – children with ASD/ASD+ADHD showed reduced right-hemispheric lateralisation of the face-sensitive N170 ERP component, while children with ADHD/ASD+ADHD showed reduced effects of face inversion on latency of the P1 component (Tye et al., 2013). In the current study, we examined effects of ASD and ADHD on the extent and organisation of oscillatory neural networks underlying face processing in the upright and inverted face conditions, focusing on the time-ranges corresponding to the P1 and N170 ERP components (described in section 2.3.4 below).

## *2.3 EEG data processing and computation of oscillatory network indices*

### *2.3.1 Pre-processing*

Data from all three paradigms were pre-processed offline using Brain Vision Analyser 2.03 (Brain Products, Munich, Germany). The same pre-processing steps were used for each task and these were performed blind to group status. The most anterior scalp electrodes, Fp1 and Fp2, were removed from all participants due to excessive muscular and ocular artefacts. Remaining channels that were flat or excessively noisy throughout recording were removed and interpolated with spherical spline interpolation using clean, immediately surrounding channels. The data were re-referenced to the average reference and filtered with 0.1Hz high-pass, 30Hz low-pass, 50Hz notch Butterworth 24dB/Oct filters. Independent component analysis (ICA) was used to identify and remove components reflecting blinks and horizontal eye movements. The data were segmented into epochs appropriate for each task: 2-second non-overlapping epochs for resting-state, -500 to +2500ms Cue-locked epochs for the CPT,

and -500ms to +1000ms upright- and inverted-face stimulus-locked epochs for the face processing task. The long (500ms) baselines for the cognitive task epochs and the long post-stimulus period in the Cue-locked attentional control task epochs were used to allow a sufficient period either side of time-ranges of interest (beginning as early as 100ms and ending as late as 1650ms post-stimulus) to enable a full coverage of these time-ranges in the time-frequency decomposition (see 2.3.4 below). Epochs with remaining artefacts, defined as those with amplitudes  $\pm 90\mu\text{V}$  or peak-to-peak amplitude change of  $200\mu\text{V}$ , were excluded from further analysis. Clean epochs in each task were exported to FieldTrip (Oostenveld, Fries, Maris & Schoffelen, 2011) within the MATLAB R2017b (The Mathworks Inc., Natick, MA) environment for computation of network measures and statistical analysis. Participants with fewer than 20 clean epochs per condition were excluded from further analysis on a task-by-task basis. The number of children included in analysis of each task, along with the mean number of epochs included per task and condition, are shown in Table 1.

### 2.3.2 *Resting-state network computation*

In FieldTrip, the 2-second resting-state epochs were subjected to Fast Fourier Transform with a 10% Hanning window taper to obtain Fourier coefficients for the 1-20Hz range at 1Hz intervals. Functional connectivity at each of these frequency steps was quantified in terms of the extent to which the phases of oscillatory signals at different electrodes were synchronised with each other by computing the debiased weighted phase lag index (dwPLI; see Vinck, Oostenveld, Van Wingerden, Battaglia & Pennartz, 2011 for mathematical formula) between each pair of electrodes across epochs. This resulted in one 60x60 adjacency matrix per frequency step per participant, where matrix element ( $ij$ ) holds the phase synchronisation (dwPLI value) of signals between  $i$  and  $j$  electrodes. The adjacency matrices were then averaged across frequency steps to obtain one 60x60 adjacency

matrix for connectivity in the delta (1-3Hz), theta (4-8Hz), alpha (8-12Hz) and beta (12-20Hz) frequency bands. The resulting matrices (four per participant) were used in statistical analysis of large-scale resting-state networks (described in section 2.4.1 below).

In addition, we computed graph theoretical metrics to characterise the organisation of resting-state networks. Graph theory describes functional brain networks as graphs characterised by nodes (brain regions or electrodes) and edges (connections between nodes, e.g. strength of oscillatory synchrony) (Sporns et al., 2004). Graph theoretical methods quantify organisational properties of such networks. Two metrics relevant to ASD and ADHD are clustering coefficient and path length. Clustering coefficient is the proportion of a node's neighbouring nodes that are connected with each other and reflects the inter-connectedness of local networks (Bullmore & Sporns, 2009; Sporns et al., 2004). Path length is the average shortest distance (number of edges) between nodes and reflects global efficiency (Bullmore & Sporns, 2009; Sporns et al., 2004). A high clustering coefficient and low path length index efficient segregation/specialisation and integration, respectively (Stam & Van Straaten, 2012). In the current study, clustering coefficient and path length were computed from adjacency matrices in each frequency band with the Brain Connectivity Toolbox (BCT, Rubinov & Sporns, 2010) and used in statistical analysis of network organisation (described in section 2.4.2 below).

### *2.3.3 Attentional control network computation*

Analysis of oscillatory networks in the CPT task was restricted to the theta and alpha frequency ranges since these frequencies have been most robustly implicated in attentional control (see Clayton, Yeung & Kadosh, 2015 for a recent review) and to limit the number of analyses conducted. In FieldTrip, the -500 to +2500ms Cue-locked epochs were subjected to Fourier analysis using an adjustable sliding time-window of 3 cycles per window and a 10%



Hanning taper to obtain Fourier coefficients for the 4-12Hz frequency range in 1Hz steps for each time-point in the epoch. Time-window length ranged from 250ms at 12Hz to 750ms at 4Hz and slid along the epoch in 50ms increments. The dwPLI was then calculated for the Fourier coefficients at each time and frequency interval. The resulting dwPLI adjacency matrices were averaged across time-points in the time-range of the Cue-P3 (400ms-700ms post-Cue onset) and CNV (1300ms-1650ms post-Cue onset). Finally, time-averaged dwPLI matrices were averaged across frequency intervals to obtain one 60x60 adjacency matrix for the Cue-P3 and CNV time-ranges in the theta (4-8Hz) and alpha (8-12Hz) frequency bands. The resulting matrices (four per participant) were used in statistical analysis of large-scale attentional networks (see section 2.4.1) and the clustering coefficient and path length were computed for each matrix in BCT and used in statistical analysis of attentional network organisation (see section 2.4.2).

### *2.3.4 Social cognition network computation*

In line with previous work reporting that oscillatory networks in the alpha and beta frequencies are most closely associated with face processing (Jaime et al., 2016; Mennella et al., 2017) and to limit the number of tests conducted, the current analysis of oscillatory networks in the face processing task focused on the alpha and beta frequency ranges. In FieldTrip, the -500 to +1000ms stimulus-locked epochs were transformed into the time-frequency domain using Fourier analysis with an adjustable sliding time-window of 3 cycles per window and a 10% Hanning taper to obtain Fourier coefficients for the 8-20Hz frequency range in 1Hz steps for each time-point in the epoch. Time-window length ranged from 15ms at 20Hz to 375ms at 8Hz and slid along the epoch in 50ms increments. dwPLI values were calculated for the Fourier coefficients at each time and frequency interval. The resulting adjacency matrices were averaged across time-points in the time-ranges of the P1 (50ms-

250ms post-stimulus) and N170 (100ms-300ms post-stimulus) and then averaged across frequency steps to obtain one 60x60 adjacency matrix for the P1 and N170 time-ranges in the alpha (8-12Hz) and beta (12-20Hz) frequency bands for each condition (upright and inverted faces). These adjacency matrices (eight per participant) were used in statistical analysis of large-scale networks underlying face processing (see section 2.4.1). Clustering coefficient and path length were computed for each matrix in BCT and used in statistical analysis of face processing network organisation (see section 2.4.2).

## *2.4 Statistical analysis*

### *2.4.1 Analysis of large-scale networks in resting-state, attentional control and social cognition task conditions*

The hypothesised effects of ASD and ADHD on large-scale oscillatory networks underlying the resting-state, attentional control and social cognition task conditions were tested using Network Based Statistic (NBS; Zalesky, Fornito & Bullmore, 2010). NBS is a non-parametric graph-theoretical statistical analysis method which identifies brain networks, defined as topologically connected clusters of nodes (electrodes here) based on the strength of their edges (indexed by dwPLI here), that differ significantly between groups or conditions while controlling for multiple comparisons (e.g. the 3,600 dwPLI values in each adjacency matrix). NBS first computes a test-statistic ( $t$ - or  $F$ -value) for each connection in the adjacency matrix, applies a primary threshold to each connection to isolate those with suprathreshold values, identifies topologically connected components (brain networks) among suprathreshold connections, and finally ascribes a  $p$ -value to identified networks via permutation testing. Covariates can be included to control for confounding variables.

We used factorial 2 x 2 NBS models with the between-subjects factors of ASD (ASD-yes: ASD and ASD+ADHD groups; ASD-no: ADHD and Control groups) and ADHD

(ADHD-yes: ADHD and ASD+ADHD groups; ADHD-no: ASD and Control groups) to test for effects of ASD (differences between children with ASD compared to those without ASD) and ADHD (differences between children with ADHD compared to those without ADHD) and any interaction between the ASD and ADHD factors on large-scale networks in each task, condition and frequency band. Significant interaction effects were further investigated using NBS to compare networks between the levels of the ASD and ADHD factors. For all NBS models, a primary threshold of 4.0 (equivalent to  $p < .05$ ) and 5,000 permutations were used. Significant brain networks ( $p < .05$ ) were visualised using BrainNet Viewer (Xia, Wang & He, 2013). Age was included as a covariate in all NBS models given known effects of age on neural networks (e.g. Boersma et al., 2011). The models were repeated including IQ and exposure to stimulant medication (categorical covariate coded as 1 = ever received stimulant medication, 0 = never received stimulants) as covariates given group differences in IQ (Table 1) and to control for any influence past use of stimulants may have had on oscillatory connectivity (Schrantee et al., 2018); the results are reported wherever they differ from the main analysis.

#### *2.4.2 Analysis of network organisation in resting-state, attentional control and social cognition task conditions*

The hypothesised effects of ASD and ADHD on the organisation of oscillatory networks underlying resting-state, attentional control and social cognition were tested in SPSS v24 (IBM Corp) using a similar approach to the NBS analysis of differences in large-scale networks. Factorial 2 (ASD-yes, ASD-no) x 2 (ADHD-yes, ADHD-no) MANCOVA models assessed the effects of ASD, ADHD and their interaction on clustering coefficient and path length for each task and condition. Separate MANCOVA models were used for clustering coefficient and path length in each task; each model included clustering coefficient

or path length measures from all frequencies and conditions for that task (e.g. one MANCOVA examined differences between the four groups in clustering coefficient across delta-beta frequencies in the resting-state task). Significant interactions were further investigated with planned pairwise contrasts between the levels of the ASD and ADHD factors with Bonferroni correction applied to control for multiple comparisons. Age was included as a covariate in all models; the models were repeated including IQ and medication exposure as additional covariates and results are reported wherever they differ from the main MANCOVAs.

### 3. Results

#### 3.1 *Resting-state*

##### 3.1.1 *Large-scale resting-state networks*

The 2 x 2 factorial NBS revealed a significant main effect of ASD on large-scale networks in the alpha range ( $p = .02$ , Figure 1a), which reflected a significantly hypoconnected network in children with ASD (ASD/ASD+ADHD) compared to those without ASD (ADHD/Controls). This effect remained significant when covarying IQ ( $p = .049$ ) but not when covarying medication exposure ( $p = .12$ ). There were no further effects of ASD and no effects of ADHD or ASD\*ADHD interactions on resting-state networks ( $p \geq .06$ ).

##### 3.1.2 *Resting-state network organisation*

Factorial MANCOVA on clustering coefficient revealed a significant main effect of ASD in the alpha range ( $F(1, 64) = 5.43, p = .02, \eta p^2 = .078$ ), with significantly lower clustering in children with ASD compared to those without ASD (Table 2). There were no further effects for clustering coefficient ( $F \leq 2.69, p \geq .11, \eta p^2 \leq .040$ ). Factorial

MANCOVA on path length revealed a significant main effect of ASD in the alpha range ( $F(1, 64) = 5.31, p = .02, \eta p^2 = .077$ ), reflecting significantly longer path length in children with ASD than children without ASD (Table 2). There were no further significant effects for path length ( $F \leq 1.64, p \geq .21, \eta p^2 \leq .025$ ). These effects remained significant when controlling for IQ ( $p \leq .04$ ) but became non-significant when covarying medication exposure ( $p \geq .10$ ).

[Figures 1 & 2]

[Table 2]

### *3.2 Attentional control task*

#### *3.2.1 Large-scale attentional networks*

In the time-range of the Cue-P3, there were significant effects of ASD ( $p = .01$ ) and ADHD ( $p = .02$ ) on large-scale networks in the theta range, reflecting significant hypoconnectivity in children with ASD/ASD+ADHD compared to ADHD/Controls (Figure 1b) and significant hyperconnectivity in children with ADHD/ASD+ADHD compared to ASD/Controls (Figure 2a). The effect of ASD remained when covarying IQ ( $p = .01$ ) and medication exposure ( $p = .003$ ); the ADHD effect remained when covarying medication exposure ( $p = .01$ ) but not when covarying IQ ( $p = .051$ ). There were no further effects of ASD or ADHD and no ASD\*ADHD interactions in the Cue-P3 time-range ( $p \geq .20$ ).

In the Cue-CNV time-range, there were significant effects of ASD ( $p = .02$ ) and ADHD ( $p = .04$ ) on large-scale networks in the theta range, reflecting a significantly hypoconnected network in children with ASD compared to those without ASD (Figure 1c) and a significantly hyperconnected network in children with ADHD compared to those without ADHD (Figure 2b). When controlling for IQ, the ASD effect remained significant ( $p = .03$ ) but the ADHD effect did not ( $p = .07$ ); neither the ASD or ADHD effect remained

when covarying medication exposure ( $p \geq .25$ ). There were no further effects in the Cue-CNV time-range ( $p \geq .30$ ).

### *3.2.2 Attentional network organisation*

Factorial MANCOVA on clustering coefficient revealed a significant main effect of ASD in the theta band during the Cue-P3 ( $F(1, 75) = 8.01, p = .006, \eta p^2 = .097$ ) and CNV ( $F(1, 75) = 4.80, p = .03, \eta p^2 = .060$ ) time-ranges, reflecting lower clustering in children with ASD than in those without ASD (Table 2). There were no further significant effects on clustering coefficient ( $F \leq 2.59, p \geq .11, \eta p^2 \leq .033$ ). These effects were unchanged when covarying IQ ( $p \leq .04$ ). The effect of ASD on clustering coefficient during the Cue-P3 time-range remained significant when covarying medication exposure ( $p = .01$ ) while the effect during the CNV time-range did not ( $p = .12$ ).

Factorial MANCOVA on path length revealed a significant main effect of ASD for the Cue-P3 time range in the theta band ( $F(1, 75) = 5.82, p = .02, \eta p^2 = .072$ ), reflecting longer path length in children with ASD than those without ASD (Table 2). There was also a significant effect of ADHD on path length for the Cue-P3 time-range in the alpha band ( $F(1, 75) = 4.59, p = .04, \eta p^2 = .058$ ), with shorter path length in children with ADHD compared to those without ADHD (Table 2). There were no further significant effects for path length ( $F \leq 2.37, p \geq .13, \eta p^2 \leq .029$ ). The effect of ASD remained significant when covarying IQ and medication exposure ( $p \leq .03$ ). The effect of ADHD remained significant when covarying medication exposure ( $p = .009$ ) but not when covarying IQ ( $p = .07$ ).

## *3.3 Social cognition networks*

### *3.3.1 Large-scale social cognition networks*

In the upright face condition, there were significant effects of ASD ( $p = .04$ ) and ADHD ( $p = .03$ ) on large-scale networks in the alpha range in the time-range of the P1, reflecting a significantly hypoconnected network in children with ASD compared to those without ASD (Figure 1d) and a significantly hyperconnected network in children with ADHD compared to those without ADHD (Figure 2c). There was also a significant main effect of ASD on large-scale networks in the alpha range in the N170 time-range in the upright face condition ( $p = .04$ ), reflecting hypoconnectivity in children with ASD compared to those without ASD (Figure 1e). These effects remained significant when covarying IQ ( $p \leq .04$ ) but not when covarying medication exposure ( $p \geq .42$ ). There were no further significant effects for the upright face condition, and no significant effects in the inverted face condition ( $p \geq .06$ ).

### 3.3.2 Social cognition network organisation

The factorial MANCOVA on clustering coefficient revealed significant effects of ASD in the beta band for the P1 time-range ( $F(1, 80) = 5.46, p = .02, \eta^2 = .064$ ) and the N170 time-range ( $F(1, 80) = 4.01, p = .049, \eta^2 = .048$ ) in the upright face condition, reflecting lower clustering in children with ASD than in those without ASD (Table 2). The effect of ASD on beta clustering in the P1 time-range remained significant when controlling for IQ and medication exposure ( $p \leq .04$ ), while the effect in the N170 time-range did not ( $p \geq .06$ ). There were no further significant effects for clustering coefficient ( $F \leq 3.75, p \geq .06, \eta^2 \leq .045$ ). The factorial MANCOVA on path length revealed no significant effects of ASD, ADHD or ASD\*ADHD interaction ( $F \leq 3.87, p \geq .053, \eta^2 \leq .046$ ) (Table 2).

## 4. Discussion

### 4.1 Task-independent hypoconnectivity in children with ASD

Children with ASD (ASD, ASD+ADHD) showed significantly hypoconnected oscillatory networks in all cognitive domains compared to those without ASD (ADHD, Controls). In the resting-state, a widespread hypoconnected network in the alpha range, lower alpha clustering coefficient (reduced local network connectivity) and longer alpha path length (reduced global network efficiency) characterised children with ASD and ASD+ADHD. In the attentional control task, during the Cue-P3 time-range associated with directing attention towards cue stimuli, children with ASD/ASD+ADHD showed an extensive hypoconnected large-scale network in the theta band, lower theta clustering coefficient (weaker local connectivity) and longer theta path length (weaker global integration) compared to children without ASD. Similarly, during the CNV time-range associated with preparing for the upcoming stimulus indicated by the cue, children with ASD/ASD+ADHD showed a widespread hypoconnected network and lower clustering coefficient in the theta range compared to those without ASD. Finally, during the social cognition task, children with ASD/ASD+ADHD showed a hypoconnected network consisting largely of long-range left-hemisphere and bilateral fronto-central connections in the alpha range during the P1 time-range associated with early visual/attentional processing of faces in the upright condition, as well as lower clustering coefficient (weaker local connectivity) in the beta frequency during this time-range. A very similar hypoconnected network in the alpha range and reduced clustering coefficient in the beta frequency were also present during the N170 face processing time-range for upright faces in children with ASD.

Previous authors have proposed that ASD is a disconnection syndrome characterised by reduced connectivity in integrative neural circuitry, which leads to deficits in higher-order cognitive functions that require the coordination of different neurocognitive processes, such as social cognition and attentional control, and the core symptoms of the disorder (Just et al., 2004). Our findings of ASD-related hypoconnectivity in large-scale networks during resting-



state and multiple higher-order attentional and social cognitive processes are consistent with this theory and suggest that reduced functional connectivity may act as a common platform for some of the diverse neurocognitive impairments associated with ASD. The frequency- and time-ranges of the tasks in which we observed hypoconnectivity largely corresponded to those in which we previously found atypicalities in resting-state oscillatory power and ERP correlates of attentional control and social cognition (Shephard et al., 2018; Tye et al., 2013; 2014a). This finding suggests that, consistent with the underconnectivity hypothesis, reduced functional integration of large-scale networks may underlie deficits in higher-order cognitive function in ASD. Importantly, while hypoconnectivity was extensive in ASD it was not generalised to all aspects of cognitive processing: in the social cognition task hypoconnectivity was present while children viewed upright faces but not during inverted face viewing. This finding is in line with recent work indicating that partially distinct networks underlie upright and inverted face processing (Rosenthal, Sporns & Avidan, 2017) and with many previous studies showing that individuals with ASD have difficulty with processing upright but not inverted faces (Nomi & Uddin, 2015).

Our findings are consistent with and extend previous research reporting hypoconnectivity in ASD during resting-state (Dickinson et al., 2018; Kikuchi et al., 2015), attentional control (Doesburg et al., 2013; Kenet et al., 2012) and social cognition (Khan et al., 2013; Mennella et al., 2017) tasks examined independently, and the one previous study (Jaime et al., 2016) reporting hypoconnectivity across resting-state and social cognition domains in ASD. However, in contrast to some previous resting-state studies (Ghuman et al., 2017; Peters et al., 2013), we found no evidence of increased local with decreased global network function in ASD. One explanation for this discrepancy is that alterations in connectivity might vary with the type of cognitive processing individuals with ASD are engaged in. Individuals with ASD might show increased local and decreased global

connectivity during aspects of cognition requiring detail-focused processing such as visual search, which has been shown to be superior in children and adults with ASD (Kaldy, Giserman, Carter & Blaser, 2016). Indeed, fMRI studies have reported increased functional connectivity during visual search in individuals with ASD (Keehn, Shih, Brenner, Townsend & Müller, 2012). An alternative explanation is that some children with ASD show widespread hypoconnectivity while others show a local-over-global imbalance. Our findings suggest this does not depend on the presence of co-occurring ADHD symptoms since the ASD+ADHD group did not show a local-over-global connectivity pattern. Further work in larger samples using a wider range of cognitive tasks, including those that individuals with ASD perform particularly well at, will be important to explore possible functional connectivity subtypes in ASD.

#### *4.2 Task-related hyperconnectivity in children with ADHD*

Children with ADHD showed hyperconnected large-scale networks in the two cognitive task conditions compared to children without ADHD. In the attentional control task, children with ADHD and ASD+ADHD showed a widespread hyperconnected network involving frontal-frontal and long-range fronto-posterior connections in the theta range and shorter path length (stronger global connectivity) in the alpha range during the Cue-P3 time-range associated with directing attention towards cue stimuli compared to children without ADHD. In the CNV time-range associated with preparing for the upcoming stimulus indicated by the cue, children with ADHD/ASD+ADHD showed a hyperconnected network in the theta range involving fronto-central and posterior connections compared to children with ASD/Controls. In the social cognition task, children with ADHD/ASD+ADHD showed a dense hyperconnected network in the alpha range during early visual/attentional processing (P1 time-range) of upright faces compared to children without ADHD. There were no

alterations in clustering coefficient associated with ADHD, suggesting that the hyperconnectivity mainly affected global rather than local network function. Importantly, there were no effects of ADHD on oscillatory networks during the resting-state, indicating that increased connectivity in ADHD is task-related rather than generalised.

The task conditions and time-ranges in which hyperconnectivity was present in ADHD were those involving attentional orienting towards cue, target and face stimuli. These were also the conditions and time-ranges in which ADHD effects on ERP correlates of attentional control (reduced Cue-P3 amplitude) and social cognition (reduced differentiation of P1 latency for upright vs. inverted faces) were most prominent in our previous work, which we interpreted as difficulties with attentional orienting in children with ADHD (Tye et al., 2013; 2014a). Together, these findings suggest that attentional engagement mechanisms during the early stages of visual processing are particularly disrupted in ADHD and that hyperconnectivity in large-scale networks could underpin this impairment. In line with this suggestion, previous authors have proposed that hyperconnectivity in ADHD reflects excessive bottom-up processing whereby incoming sensory information inundates circuitry responsible for top-down executive processes and prevents efficient attentional control (Heinrichs-Graham et al., 2014).

Our attentional control findings are consistent with previous studies reporting increased oscillatory connectivity, particularly in frontal-frontal and frontal-posterior connections, in individuals with ADHD compared to typically developing controls during attentional control tasks (Heinrichs-Graham et al., 2014; Silberstein et al., 2016). We extend this work by showing that the same pattern of hyperconnectivity in large-scale oscillatory networks is also present during social cognition tasks in which functional connectivity has not previously been investigated in ADHD. However, our findings of unaltered connectivity during the resting-state are inconsistent with several previous studies reporting increased

resting-state connectivity in children and adults with ADHD (Barry et al., 2002; 2005; Robbie et al., 2016). Still, other recent studies have also found no alterations in resting-state oscillatory connectivity in children with ADHD (Alba et al., 2016) and, similar to our connectivity findings, recent work on oscillatory power reports that atypicalities in oscillatory activity are restricted to task-states rather than baseline or resting-states in individuals with ADHD (Skirrow et al., 2015). We also found no evidence of reduced global or long-range connectivity in ADHD, which is in contrast to previous resting-state (Barry et al., 2002; 2005; Murias et al., 2006; Robbie et al., 2016) and attentional control (Liu et al., 2015; Mazaheri et al., 2010) studies in children with ADHD of the same age as those in our sample. This discrepancy might reflect differences in methodology since most of those previous studies (except Liu et al., 2015) examined connectivity between specific pairs of electrodes and used connectivity metrics based on or influenced by oscillatory power, in contrast to our study in which we used a phase-based metric of connectivity and examined synchrony in large-scale networks. Another explanation, at least for the differences in attentional control findings, is that the tasks used previously by Liu et al. (2015) and Mazaheri et al. (2010) were more complex and required a greater level of attentional control (e.g. switching attention between sensory modalities, inhibiting interfering stimuli) than our Cue condition which simply required attending to a stimulus and preparing a response. Future work will be needed to examine whether hyperconnectivity during early stages of attentional orienting is followed by reduced functional connectivity in top-down control circuitry required in later stages of attentional control. Finally, like ASD, ADHD is a heterogeneous disorder and it is possible that functional connectivity subtypes exist.

#### *4.3 ASD- and ADHD-related connectivity alterations in children with ASD+ADHD*

Our findings in the ASD and ADHD groups indicate that these disorders can be dissociated (at least in our sample) based on atypicalities in oscillatory functional neural networks, with task-independent hypoconnectivity in the children with ASD and task-related hyperconnectivity in the children with ADHD. We found no significant interactions between the ASD and ADHD group factors, indicating that the children with both disorders did not differ from children with ASD when paired with this group and vice versa when paired with the ADHD group. This pattern of findings suggests that the children with co-occurring ASD+ADHD showed both ASD-like hypoconnectivity and ADHD-like hyperconnectivity. These findings may help in understanding the aetiology of co-occurring ASD+ADHD. Several models of comorbidity have been proposed to account for the co-occurrence of these disorders, including that ASD and ADHD are different manifestations of one overarching condition, two independent disorders that co-occur ('true comorbidity'), or that co-occurring ASD+ADHD represents a third clinical entity with its own pathophysiological basis (Rommelse, Geurts, Franke, Buitelaar & Hartman, 2011; Taurines et al., 2012). Our connectivity findings are most in line with the second model since the independent alterations associated with ASD and ADHD were summed in an additive manner in children with ASD+ADHD. However, future replication in other samples, particularly in large samples with greater power to detect interaction effects between ASD and ADHD group factors, is necessary. Our findings may also have clinical implications for treating individuals with co-occurring ASD+ADHD. For instance, EEG- and fMRI-based neurofeedback training of aberrant functional connectivity have been proposed as potential treatment options for ASD (Coben & Myers, 2008; Pineda, Carrasco, Datko, Pillen & Schalles, 2016) and ADHD (Russell-Chapin et al., 2013). However, neurofeedback therapies designed to increase hypoconnectivity in ASD are unlikely to improve ADHD symptoms and may exacerbate

ADHD-related hyperconnectivity, and vice versa for neurofeedback training designed to reduce hyperconnectivity in ADHD.

#### *4.4 Neural mechanisms underlying hypo-/hyper-connectivity in ASD and ADHD*

It is important to note that while our findings increase understanding of the type of large-scale neural network alterations associated with ASD and ADHD and how they might relate to other neurocognitive atypicalities, the neurobiological mechanisms underlying atypically decreased and increased connectivity in these disorders are still not clear. It has been suggested that neural connectivity disturbances may arise from alterations in the balance of glutamatergic excitatory and GABA-ergic inhibitory signalling at the micro-circuit level (Foss-Feig et al., 2017). Specifically, Foss-Feig et al. (2017) set out the different ways in which excitatory/inhibitory (E/I) signalling could be altered and how this in turn might cause functional connectivity disturbances in different neurodevelopmental disorders. For example, reduced E/I ratio was suggested to result in low spontaneous neural activity and narrowly-tuned and poorly integrated circuits which are unable to function efficiently (Foss-Feig et al., 2017). An increased E/I ratio, on the other hand, would lead to increased spontaneous random signalling and disorganised and inefficient neural circuits, as well as hyperactive responses to basic sensory stimulation (Foss-Feig et al., 2017). Considering these accounts with our connectivity findings, it seems plausible that a reduced E/I ratio might underlie the hypoconnectivity in ASD and an increased E/I ratio could underpin the hyperconnectivity in ADHD. It will be important for future work to examine how E/I signalling alterations relate to atypicalities in oscillatory network function in ASD and ADHD. This knowledge could be used to develop more effective pharmacological treatments for children with these disorders.

#### *4.5 Limitations*

Several limitations to this study should be considered. First, we report on scalp-level rather than source-level analyses, which complicates interpretation of our findings due to possible effects of volume conduction on scalp-level networks. We used the dwPLI connectivity metric and graph theoretical methods which are less sensitive to effects of volume conduction than other connectivity methods (Bullmore & Sporns, 2009; Sporns et al., 2004; Vinck et al., 2011), but still we encourage replication of our network findings in source-space (McLoughlin, Palmer, Rijdsdijk & Makeig, 2014). High levels of muscular artefact precluded analysis of high-frequency gamma synchrony in our sample. Gamma synchrony is believed to mediate short-range local networks (Siegel et al., 2012; Uhlhaas & Singer, 2006), and has been shown to be abnormal in ASD (Kitzbichler et al., 2016). This limitation may explain why we did not find evidence of increased local-over-global network processing in ASD and should be addressed in future research. We excluded participants receiving medications other than stimulants and ensured that participants receiving stimulants underwent a 48-hour wash-out period prior to EEG testing. Nevertheless, a considerable proportion of the children in our ADHD and ASD+ADHD groups had been exposed to stimulant medication (38% and 24%, respectively). This is important since recent work suggests that stimulant medication, even if not currently used, may have long-lasting effects on prefrontal brain function and dopaminergic signalling (Schrantee et al., 2018). It is therefore possible that medication exposure in our ADHD and ASD+ADHD groups influenced the patterns of oscillatory connectivity associated with ADHD. Indeed, covarying for medication exposure did reduce the significance of some of our connectivity findings, suggesting that past stimulant use may have affected connectivity in these children. Future research in larger samples of never-medicated compared to stimulant-exposed children will be needed to rigorously assess the effects of stimulant medication on neural connectivity patterns associated with ADHD. Our analysis of neural networks was conducted at one time-

point only and after the emergence of clinical symptoms of ASD and ADHD. Future prospective longitudinal studies will be important to understand both how connectivity alterations might change over time in ASD and ADHD, and also whether atypicalities in neural network function precede the development of overt symptoms. While the latter question has been addressed in the ASD field, with several studies reporting functional connectivity alterations in infancy that predict later ASD symptoms (e.g. Bosl, Tager-Flusberg & Nelson, 2018; Orekhova et al., 2014), no published work has examined whether the same is true for ADHD. Finally, the sample sizes for our participant groups were modest, particularly after exclusions following pre-processing of the EEG data, and we intentionally reduced heterogeneity by studying only boys of a limited age-range. The small sample sizes and limited heterogeneity within our participant groups may explain why our connectivity findings contrast with some previous research, for example the absence of increased local and decreased global connectivity in the ASD groups. Consequently, our results should be considered as preliminary and future research with larger samples, including girls with ASD and ADHD, will be needed to assess the generalisability of our findings.

## 5. Conclusion

This study is the first to compare oscillatory neural networks across resting-state, attentional control and social cognition domains between children with ASD, ADHD, ASD+ADHD, and typical development. Children with ASD with and without co-occurring ADHD symptoms showed hypoconnectivity in large-scale networks as well as altered network organisation in all three cognitive domains compared to children without ASD. In contrast, children with ADHD with and without co-occurring ASD symptoms showed hyperconnectivity in large-scale networks that was restricted to cognitive task conditions compared to children without ADHD. These novel findings indicate that ASD and ADHD



may be dissociable based on alterations in oscillatory neural networks, and that such alterations may underlie a range of neurocognitive atypicalities associated with these disorders. Children with ASD+ADHD showed hypoconnectivity compared to children without ASD and hyperconnectivity compared to children without ADHD, indicating that ASD- and ADHD-related alterations in large-scale oscillatory networks are summed in children with both disorders.

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## Data statement

In the Supplementary Materials we provide detailed information to enable the exact replication of our analyses. Accompanying MATLAB code, SPSS outputs containing summary statistics and statistical test results, and all other study materials (with exceptions noted below) are available to download from the public OSF data repository here: <https://osf.io/eg9wd/>. Our ethical approval for this study does not include permission to upload data files to a public data repository and parents of children participating in the study only consented to their child's data being shared with scientists outside of the research team if those scientists were working collaboratively with the study team. Thus, scientists and others interested in accessing the data files should email the authors ([charlotte.tye@kcl.ac.uk](mailto:charlotte.tye@kcl.ac.uk) and [elizabeth.1.shephard@kcl.ac.uk](mailto:elizabeth.1.shephard@kcl.ac.uk)) and state their reason(s) for requesting the data (e.g. to replicate the analyses reported in this paper) and their agreement to work collaboratively with the study team (i.e. by keeping the study team informed of analysis methods and results). Provided there is a reason for accessing the data, e.g. to conduct a replication analysis, and the individual agrees to keep the study team informed of analysis methods and results, the authors will agree to collaborate with the individual and full access to the data files will be granted. Access to the data files will not be granted if no reason is given for requesting the

data and/or if the individual interested in accessing the data does not agree to keep the study team informed of analysis plans and results. The experimental tasks used in this study (upright and inverted face processing task and CPT-OX task) were developed by scientists outside of the study team and were used in this study after seeking permission from those scientists. For this reason, we have not uploaded the programme files and stimuli for the experiments to the OSF repository; individuals wishing to access the stimuli and experimental programme files should request these from the original authors (email Leslie Tucker at the Centre for Brain and Cognitive Development, [l.tucker@bbk.ac.uk](mailto:l.tucker@bbk.ac.uk), to access the face processing task and Prof Daniel Brandeis at the Central Institute for Mental Health, [daniel.brandeis@zi-mannheim.de](mailto:daniel.brandeis@zi-mannheim.de), to access the CPT-OX). The procedures and analysis methods for this study were not pre-registered.

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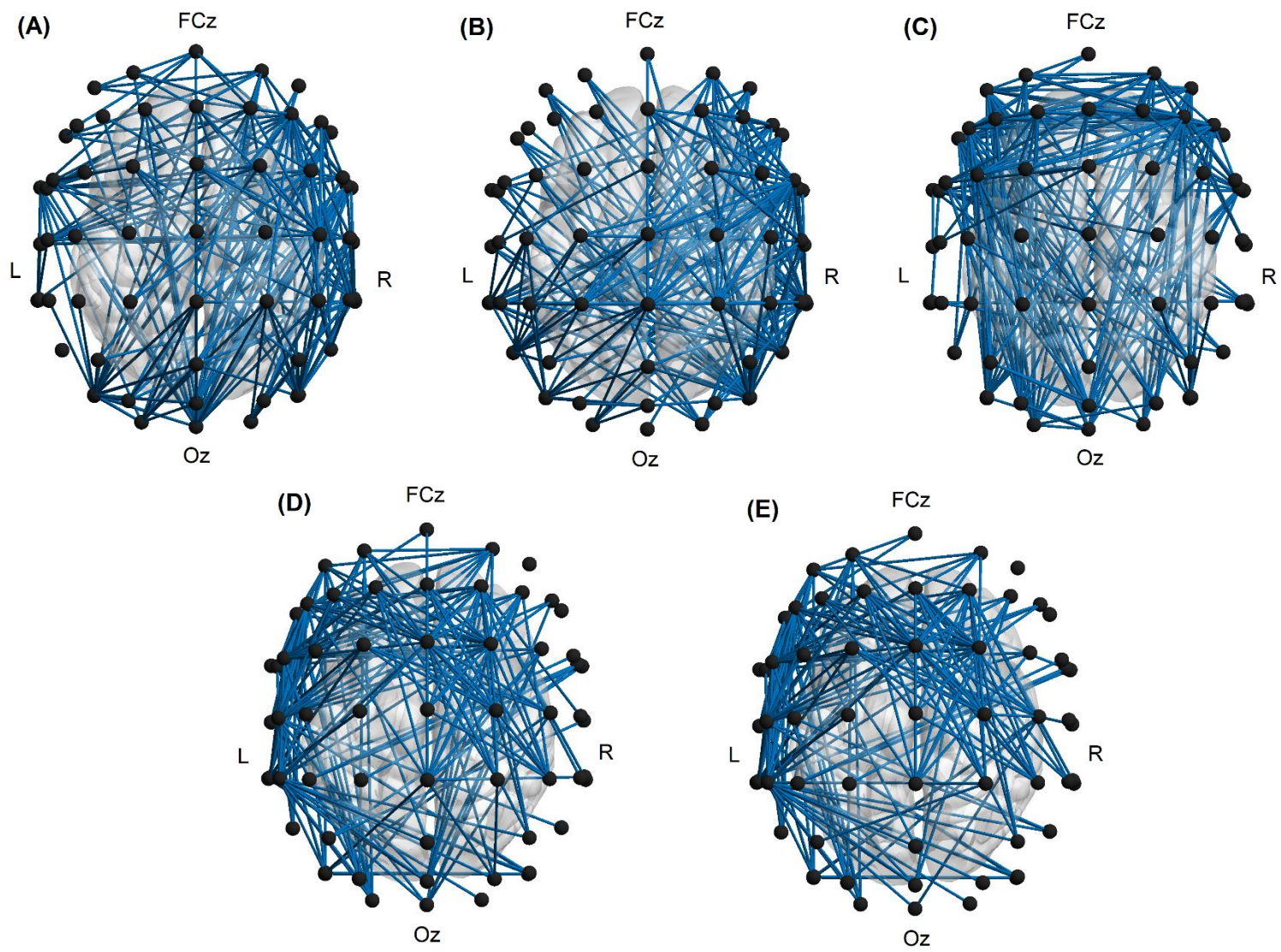
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**Table 1** Group characteristics

	ASD ( <i>n</i> = 19)	ADHD ( <i>n</i> = 18)	ASD+ADHD ( <i>n</i> = 29)	Controls ( <i>n</i> = 26)	Group differences
<i>Age (months)</i>	140.32 (20.40)	125.78 (22.92)	126.31 (20.27)	126.69 (21.47)	n/s
<i>WASI FSIQ</i>	115.68 (15.73)	104.11 (14.23) <sup>a</sup>	109.72 (13.41) <sup>a</sup>	120.04 (13.42) <sup>b</sup>	$F(3, 88) = 5.31, p = .002, \eta p^2 = .153$
<i>Hyp/Imp</i>	66.11 (12.99) <sup>a</sup>	87.89 (3.25) <sup>b</sup>	84.00 (7.63) <sup>b</sup>	58.88 (17.02) <sup>a</sup>	$F(3, 88) = 32.76, p < .001, \eta p^2 = .528$
<i>Inattention</i>	67.11 (14.13) <sup>a</sup>	83.94 (7.41) <sup>b</sup>	80.21 (11.59) <sup>b</sup>	56.08 (11.05) <sup>c</sup>	$F(3, 88) = 29.85, p < .001, \eta p^2 = .504$
<i>SCQ</i>	20.11 (6.42) <sup>a</sup>	10.89 (5.36) <sup>a</sup>	24.59 (5.71) <sup>b</sup>	3.88 (3.54) <sup>c</sup>	$F(3, 88) = 80.14, p < .001, \eta p^2 = .732$
<b><i>Resting-state</i></b>					
<i>N participants</i>	16	15	19	19	
<i>N epochs</i>	123.94 (47.81)	126.80 (47.57)	138.21 (44.10)	137.79 (49.10)	n/s
<b><i>Attentional control</i></b>					
<i>N participants</i>	18	15	23	24	
<i>N Cue epochs</i>	50.94 (15.56)	50.40 (14.61)	55.88 (12.06)	57.50 (8.70)	n/s
<b><i>Social cognition</i></b>					
<i>N participants</i>	18	15	28	24	
<i>N Upright face epochs</i>	60.28 (13.13)	58.33 (15.72)	62.57 (11.69)	65.00 (9.67)	n/s
<i>N Inverted face epochs</i>	56.72 (14.63)	56.73 (14.81)	60.86 (13.63)	63.54 (10.05)	n/s

Groups marked with different superscript letters (a, b, c) differed significantly with Bonferroni correction applied ( $p < .05$ ). *WASI FSIQ* = Wechsler Abbreviated Scale of Intelligence –Full-Scale IQ. *Hyp/Imp* and *Inattention* = Conners 3 Parent-rated Short Form Hyperactivity/Impulsivity and Inattentive T-scores. *SCQ* = Social Communication Questionnaire total score. *N participants* = the number of participants included in analysis of each task condition following exclusions due to EEG artefact. *N epochs* = the number of artefact-free epochs included in analysis in each task and condition.

**Figure 1** Effects of ASD on large-scale networks during resting-state, attentional control and face processing tasks





Plots show the large-scale networks that were significantly hypoconnected in children with ASD (ASD/ASD+ADHD) compared to children without ASD (ADHD/Controls) while controlling for age in Network Based Statistic (NBS). Panel (A) shows the hypoconnected network in the alpha range during the resting-state task. Plots (B) and (C) show the hypoconnected networks in the theta range during the attentional control task; plot (B) shows the network during the Cue-P3 time-range associated with attentional orienting to Cue stimuli, and plot (C) shows the network during the CNV time-range associated with preparing for the upcoming target stimulus. Plots (D) and (E) show the hypoconnected networks in the alpha range during the face-processing social cognition task; plot (D) shows the network during the early visual processing P1 time-range and plot (E) shows the network during the face-sensitive N170 time-range. All connections in these networks had lower synchrony (lower dwPLI values) in children with ASD compared to those without ASD.

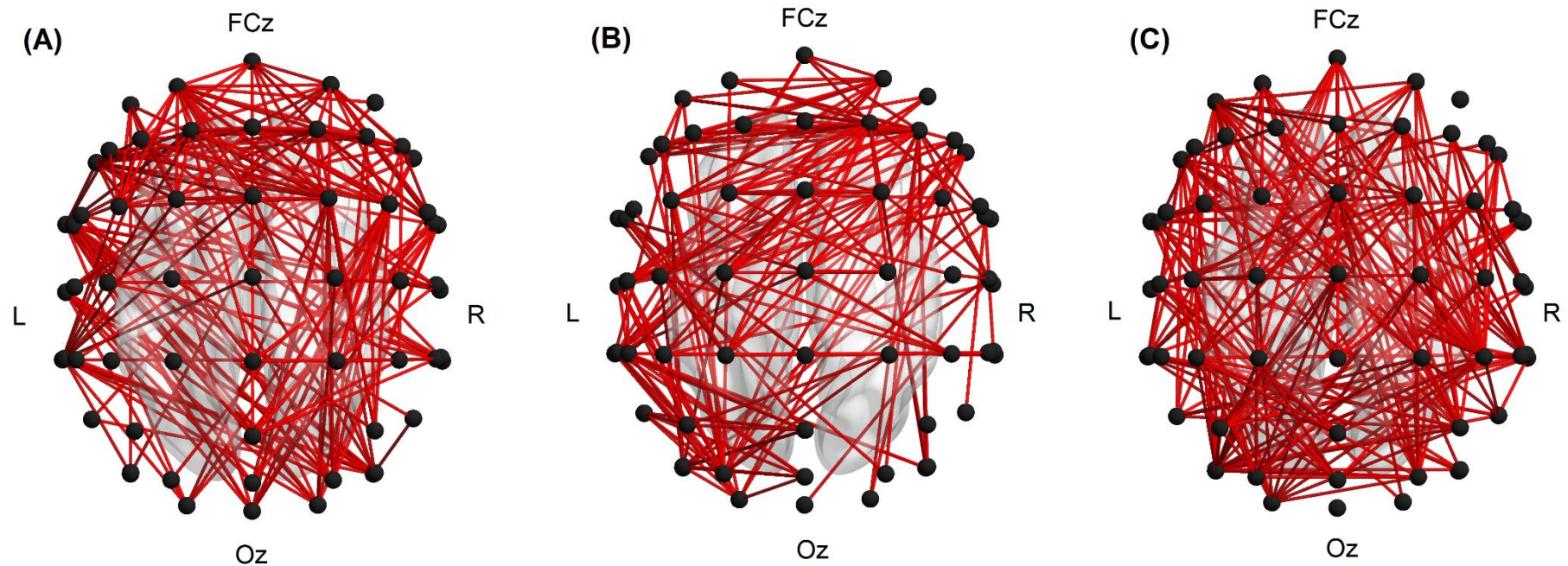
**Table 2** Clustering coefficient (CC) and path length (PL) indices of network organisation by task, condition, frequency and group

	<b>ASD</b>	<b>ADHD</b>	<b>ASD+ADHD</b>	<b>Controls</b>
<b><i>Resting-state</i></b>				
<i>Delta CC</i>	.44 (.08)	.47 (.13)	.42 (.09)	.46 (.07)
<i>Theta CC</i>	.51 (.07)	.57 (.13)	.52 (.10)	.54 (.10)
<i>Alpha CC</i>	.53 (.09)	.60 (.13)	.51 (.15)	.58 (.12)
<i>Beta CC</i>	.37 (.15)	.42 (.17)	.33 (.16)	.37 (.13)
<i>Delta PL</i>	1.67 (.10)	1.65 (.18)	1.75 (.16)	1.65 (.11)
<i>Theta PL</i>	1.62 (.13)	1.51 (.16)	1.59 (.14)	1.56 (.13)
<i>Alpha PL</i>	1.56 (.13)	1.50 (.19)	1.63 (.25)	1.50 (.16)
<i>Beta PL</i>	1.87 (.33)	1.85 (.43)	2.08 (.51)	1.98 (.31)
<b><i>Attentional control</i></b>				
<i>Cue-P3 Theta CC</i>	.60 (.07)	.67 (.09)	.58 (.09)	.62 (.09)
<i>Cue-P3 Alpha CC</i>	.57 (.09)	.60 (.10)	.57 (.07)	.58 (.10)
<i>Cue-P3 Theta PL</i>	1.49 (.11)	1.40 (.13)	1.51 (.11)	1.47 (.13)
<i>Cue-P3 Alpha PL</i>	1.55 (.16)	1.49 (.11)	1.52 (.10)	1.55 (.14)
<i>Cue-CNV Theta CC</i>	.59 (.08)	.60 (.11)	.53 (.08)	.61 (.10)
<i>Cue-CNV Alpha CC</i>	.60 (.10)	.58 (.10)	.57 (.08)	.58 (.11)
<i>Cue-CNV Theta PL</i>	1.50 (.10)	1.50 (.15)	1.60 (.16)	1.49 (.17)
<i>Cue-CNV Alpha PL</i>	1.52 (.17)	1.54 (.14)	1.56 (.13)	1.54 (.17)
<b><i>Social cognition</i></b>				
<i>Upright P1 Alpha CC</i>	.58 (.10)	.64 (.12)	.57 (.11)	.57 (.10)
<i>Upright P1 Beta CC</i>	.48 (.12)	.55 (.07)	.49 (.10)	.50 (.09)
<i>Upright P1 Alpha PL</i>	1.48 (.13)	1.44 (.17)	1.51 (.13)	1.51 (.14)
<i>Upright P1 Beta PL</i>	1.61 (.18)	1.53 (.08)	1.61 (.15)	1.62 (.14)
<i>Upright N170 Alpha CC</i>	.59 (.10)	.65 (.13)	.57 (.10)	.58 (.10)
<i>Upright N170 Beta CC</i>	.49 (.12)	.54 (.08)	.48 (.11)	.50 (.08)
<i>Upright N170 Alpha PL</i>	1.48 (.14)	1.45 (.19)	1.51 (.13)	1.50 (.15)
<i>Upright N170 Beta PL</i>	1.60 (.17)	1.56 (.08)	1.64 (.19)	1.61 (.13)

<i>Inverted P1 Alpha CC</i>	.63 (.09)	.61 (.12)	.61 (.11)	.58 (.12)
<i>Inverted P1 Beta CC</i>	.53 (.09)	.53 (.09)	.51 (.09)	.50 (.13)
<i>Inverted P1 Alpha PL</i>	1.44 (.13)	1.47 (.19)	1.45 (.13)	1.51 (.19)
<i>Inverted P1 Beta PL</i>	1.54 (.11)	1.57 (.13)	1.61 (.17)	1.60 (.21)
<i>Inverted N170 Alpha CC</i>	.63 (.10)	.64 (.11)	.61 (.11)	.59 (.12)
<i>Inverted N170 Beta CC</i>	.53 (.10)	.55 (.08)	.50 (.11)	.49 (.14)
<i>Inverted N170 Alpha PL</i>	1.44 (.15)	1.42 (.15)	1.46 (.15)	1.48 (.17)
<i>Inverted N170 Beta PL</i>	1.54 (.12)	1.55 (.11)	1.61 (.18)	1.60 (.19)

Group means (SDs) for clustering coefficient (CC) and path length (PL) are shown for each group in each task, condition, time-range and frequency band. *Cue-P3* = time-range of the P3 ERP component (400-700ms post-Cue onset) in the Cue condition of the attentional control task. *Cue-CNV* = time-range of the Cue Contingent Negative Variation (CNV) ERP component (1300-1650ms post-Cue onset) in the Cue condition of the attentional control task. *Upright* = upright face condition. *Inverted* = Inverted face condition. *P1* = time-range of the P1 ERP component (50-250ms post-stimulus onset) to face stimuli in the social cognition task. *N170* = time-range of the N170 ERP component (100-300ms post-stimulus onset) to face stimuli in the social cognition task.

**Figure 2** Effects of ADHD on large-scale networks during attentional control and social cognition tasks



Plots show the large-scale networks that were significantly hyperconnected in children with ADHD (ADHD/ASD+ADHD) compared to children without ADHD (ASD/Controls) while controlling for age in Network Based Statistic (NBS). Panels (A) and (B) show the hyperconnected networks in the theta range during the attentional control task; plot (A) shows the network during the Cue-P3 time-range associated with attentional orienting to Cue stimuli, and plot (B) shows the network during the CNV time-range associated with preparing for the upcoming target stimulus. Plot (C) shows the hyperconnected network in the alpha range during the early visual processing of upright faces (P1 time-range) of the face-processing social cognition task. All connections in these networks had stronger synchrony (higher dwPLI values) in children with ADHD compared to those without ADHD.

## Supplementary materials

### *Behavioural performance*

In the main text we report on effects of ADHD and ASD diagnosis on oscillatory neural networks during three task conditions: resting-state, social cognition and attentional control. It is possible that the extent to which participants engaged in the two cognitive tasks may have influenced their oscillatory neural network activity. In this supplementary document we therefore present the behavioural data collected alongside electroencephalographic (EEG) recordings. Since the social cognition task was a passive viewing task, there were no behavioural data. However, notes from our EEG recording sessions indicate that none of the participants included in the current analysis had difficulty paying attention or engaged poorly in this task.

Behavioural data were collected during the attentional control (CPT-OX) task (McLoughlin et al., 2010; Tye et al., 2014). Participants viewed letter-string stimuli (e.g. XDX) presented for 150ms every 1650ms. Cue stimuli (XOX, 80 trials) indicated that the next stimulus could either be a Target (OXO) for which participants were required to press a response-button (40 'Go' trials), or a non-target (e.g. XDX) for which participants withheld their responses (40 'Nogo' trials). Distractor stimuli (e.g. XHX, ODO, 240 trials) were presented amongst the Cue, Go and Nogo stimuli to increase attentional demands. Performance was assessed using the following measures: reaction time (RT) to Go target stimuli (mean RT, ms, on Go trials), error rates for Go and Nogo stimuli (% of omitted Go responses and % of committed (incorrectly responded to) Nogo stimuli, respectively), and variability of Go RTs (coefficient of variation: standard deviation of mean Go RT/mean Go RT). One child with ADHD and two children with ASD+ADHD produced excessively high Go omission error rates ( $\geq 70\%$  of Go trials) and were excluded from all (behavioural and connectivity) analyses. Group means for performance measures are shown in Table S1.

Effects of ASD and ADHD on performance were assessed using a factorial 2 (ASD-yes, ASD-no) x 2 (ADHD-yes, ADHD-no) MANOVA which included all performance measures as dependent variables. There was a significant main effect of ADHD on RT variability ( $F(1, 73) = 4.38, p = .04, \eta^2 = .057$ ) and a trend-level effect of ADHD on Go omission errors ( $F(1, 73) = 3.73, p = .06, \eta^2 = .049$ ), reflecting significantly more variable RTs to Go stimuli and a tendency for more Go omission errors in children with ADHD compared to children without ADHD. There were no further significant or trend-level effects (all  $F \leq 1.14, p \geq .29, \eta^2 \leq .015$ ).

**Table S1** Performance in the attentional control task. Group means (SDs) are presented.

	ASD	ADHD	ASD+ADHD	Controls
<i>Go RT (ms)</i>	446.89 (70.37)	465.56 (75.95)	497.58 (96.83)	480.54 (113.37)
<i>Go errors (%)</i>	3.33 (3.36)	4.19 (3.04)	4.67 (3.94)	2.17 (2.43)
<i>Nogo errors (%)</i>	4.61 (4.54)	5.40 (8.04)	6.39 (7.76)	4.29 (3.85)
<i>RT variability</i>	0.31 (0.05)	0.34 (0.09)	0.32 (.06)	0.28 (0.07)

### *Analysis protocol*

In the following we provide detailed information to enable the exact replication of our analyses. Accompanying MATLAB code, SPSS outputs containing summary statistics and statistical test results, and all other study materials (with exceptions noted below) are available to download from the public OSF data repository here: <https://osf.io/eg9wd/>. Our ethical approval for this study does not include permission to upload data files to a public data repository and parents of children participating in the study only consented to their child's data being shared with scientists outside of the research team if those scientists were working collaboratively with the study team. Thus, scientists and others interested in accessing the data files should email the authors ([charlotte.tye@kcl.ac.uk](mailto:charlotte.tye@kcl.ac.uk) and [elizabeth.1.shephard@kcl.ac.uk](mailto:elizabeth.1.shephard@kcl.ac.uk)) and state their reason(s) for requesting the data (e.g. to

replicate the analyses reported in this paper) and their agreement to work collaboratively with the study team (i.e. by keeping the study team informed of analysis methods and results). Provided there is a reason for accessing the data, e.g. to conduct a replication analysis, and the individual agrees to keep the study team informed of analysis methods and results, the authors will agree to collaborate with the individual and full access to the data files will be granted. Access to the data files will not be granted if no reason is given for requesting the data and/or if the individual interested in accessing the data does not agree to keep the study team informed of analysis plans and results. The experimental tasks used in this study (upright and inverted face processing task and CPT-OX task) were developed by scientists outside of the study team and were used in this study after seeking permission from those scientists. For this reason, we have not uploaded the programme files and stimuli for the experiments to the OSF repository; individuals wishing to access the stimuli and experimental programme files should request these from the original authors (email Leslie Tucker at the Centre for Brain and Cognitive Development, [l.tucker@bbk.ac.uk](mailto:l.tucker@bbk.ac.uk), to access the face processing task and Prof Daniel Brandeis at the Central Institute for Mental Health, [daniel.brandeis@zi-mannheim.de](mailto:daniel.brandeis@zi-mannheim.de), to access the CPT-OX).

### *EEG data processing and analysis pipeline*

The following processing and analysis pipeline was applied to the raw EEG data files; steps are detailed in the order in which they were applied to the data. Steps 1-9 were conducted in *Brain Vision Analyzer v2.03* (Brain Products, Munich, Germany); steps 10-12 were conducted in open-source *FieldTrip* (version 20180104, Oostenveld et al., 2011, <http://www.fieldtriptoolbox.org/>) and *Brain Connectivity Toolbox (BCT)* (Rubinov & Sporns, 2010, <https://sites.google.com/site/bctnet/>) software within the *MATLAB R2017b* (The Mathworks Inc., Natick, MA) environment; step 13 was conducted using the open-source

MATLAB-based toolbox *Network Based Statistic* (NBS, Zalesky et al., 2010, <https://sites.google.com/site/bctnet/comparison/nbs>); step 14 was conducted using the *Brain Net Viewer* open-source MATLAB-based toolbox (Xie et al., 2013, <https://www.nitrc.org/projects/bnv/>); step 15 was conducted in SPSS v24 (IBM Corp.).

- 1) Visual inspection of raw EEG, noting any bad channels; channels were considered bad if they were flat or showed high frequency noise for  $\geq 25\%$  of the recording.
- 2) Removal of electrodes Fp1 and Fp2 from all files and any other channels identified as bad using the *Edit Channels* transformation.
- 3) Interpolation of bad channels (but not Fp1 and Fp2 because they do not have neighbouring channels surrounding them to allow interpolation) using the *Topographic Interpolation* transformation and specifying the following settings: *Interpolation by spherical splines, Order of Splines = 4, Maximal Degree of Legendre Polynomials = 10, Default Lambda, Keep Old Channels*.
- 4) Re-reference to the average of all channels and re-acquire the online reference (FCz) using the *New Reference* transformation.
- 5) Filter using the *IIR Filters* transformation and specifying the following settings: *low cut-off = 0.1Hz, high cut-off = 30Hz, notch = 50Hz, slope of low-pass and high-pass filters = 24 dB/octave*.
- 6) Identify and remove ocular artefacts using the *ICA (Independent Components Analysis)* transformation and specifying the following: *Enable all channels, Number of components = 30, Data used to compute the ICA matrix = Interval, Sphering = Classic PCA, ICA = Fast ICA, Restricted, Ordering = Energy, Semiautomatic mode*. Components were manually reviewed for their topography and waveform shape to identify and remove components reflecting eye blinks and horizontal eye movements (range of number of components removed = 2-8).



- 7) Segmentation of data into epochs using the *Segmentation* transformation. Resting state data were segmented into equal-sized 2-second epochs by specifying the following: *Divide data set in equal sized segments, No overlapping epochs, Size of segments = Based on time (2s)*. CPT task data were segmented into Cue-locked epochs by specifying the following: *Create new segments based on marker position, No overlapping segments, Stimulus marker "4", Start and end of segments relative to position of the relevant markers = Based on time (Start = -500; End = 2500)*. Face processing task data were segmented into upright and inverted face stimulus-locked epochs by specifying the following: *Create new segments based on marker position, No overlapping segments, Stimulus markers "S90" (Upright) and "S120" (Inverted), Start and end of segments relative to position of the relevant markers = Based on time (Start = -500; End = 1000)*.
- 8) Remove remaining artefacts using the *Artifact Rejection* transformation and specifying the following: *Automatic, Enable all channels, Criteria > Amplitude = Check maximal and minimal amplitude (Minimal = -90 $\mu$ v, Maximal = 90 $\mu$ v, Mark as bad 200ms before & after event), Criteria > Max-Min (x) = Check maximal difference of values in intervals (200 $\mu$ v maximal allowed difference in 200ms interval)*.
- 9) Export cleaned epochs to ASCII format using the *Generic Data Export* function and specifying the following: *File extension = .eeg, Write header and marker files, Orientation = MULTIPLEXED, Line delimiter = CRLF (PC style), Write channel names, Export all channels*.
- 10) Import the pre-processed data into FieldTrip using the FieldTrip functions *ft\_trialfun\_general*, *ft\_definetrial*, and *ft\_preprocessing*. See Step 2 of the MATLAB scripts *BioNeD\_RestingState\_ConnectivityScript\_FinalFeb2019*,

*BioNeD\_AttentionalControl\_ConnectivityScript\_FinalFeb2019*, and

*BioNeD\_FaceProc\_ConnectivityScript\_FinalFeb2019*.

- 11) Compute fourier coefficients using the FieldTrip function *ft\_freqanalysis*, compute the debiased weighted phase lag index (dwPLI) using the FieldTrip function *ft\_connectivityanalysis*, and take the average dwPLI over frequency bands and time-ranges as appropriate for each task (defined in the main text methods) using the FieldTrip function *ft\_selectdata*. Save the connectivity matrices as .txt files for analysis in NBS. See Step 3 of the MATLAB scripts for each task.
- 12) Compute graph metrics – clustering coefficient and path length – using the FieldTrip function *ft\_networkanalysis* which calls the BCT and write outputs to excel for analysis in SPSS. See Step 4 of the MATLAB scripts for each task.
- 13) Analysis of large-scale networks using NBS specifying the following: *Statistical test = F-test, threshold = 4.0, permutations = 5000, significance = 0.05, method = Network-Based Statistic (NBS), connectivity matrices = enter the file-path for where the .txt file connectivity matrices are stored*. Node coordinates for the 64-channel Brain Vision system, channel names, and design matrices (.txt files) to model factorial effects of ASD, ADHD and their interaction (with age, IQ and medication exposure as covariates) are available in the OSF data repository. The *Contrast* field should be completed as indicated in Figure S1.
- 14) Visualise significant networks in Brain Net Viewer. Node and edge files for the significant networks reported in the main text are available in the OSF repository.
- 15) SPSS analysis of graph measures using MANCOVA (details described in the main text methods). SPSS outputs showing summary statistics and MANOVA results for clustering coefficient and path length in each task are available in the OSF data repository.

**Figure S1** NBS contrast settings

1<sup>st</sup> digit models the intercept  
2<sup>nd</sup> digit models the first group factor  
(here, ASD)  
3<sup>rd</sup> digit models the second group  
factor (here, ADHD)  
4<sup>th</sup> digit models the interaction  
between the group factors  
(ASD\*ADHD)  
5<sup>th</sup> digit models the covariate (add  
additional digits for additional  
covariates)

For example:

[0 1 0 0 0] models effect of ASD  
[0 0 1 0 0] models effect of ADHD  
[0 0 0 1 0] models interaction  
[0 1 0 0 0 0] models effect of ASD with  
two covariates

The screenshot shows the NBS v1.2 software window. The 'Statistical Model' section has a 'Design Matrix' field, a 'Contrast' field containing '[0 1 0 0 0]' (highlighted with a red circle and an arrow from the text box on the left), a 'Statistical Test' dropdown set to 'F-test', and a 'Threshold' field set to '4.0'. The 'Data' section includes fields for 'Connectivity Matrices', 'Node Coordinates (MNI)', and 'Node Labels [opt]'. The 'Advanced Settings' section includes 'Exchange Blocks [opt]', 'Permutations' set to '5000', 'Significance' set to '0.05', 'Method' set to 'Network-Based Statistic (NBS)', and 'Component Size' set to 'Extent'. A status bar at the bottom shows 'Ready...' and copyright information. The 'nbs CONNECTOME' logo is in the bottom right corner.

## References

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